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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,600	09/15/1999	ALAN BERRY	3161-18-PUS	5327
22442	7590	08/14/2006	EXAMINER	
SHERIDAN ROSS PC 1560 BROADWAY SUITE 1200 DENVER, CO 80202			FRONDA, CHRISTIAN L	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 08/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/341,600

Applicant(s)

BERRY ET AL.

Examiner

Christian L. Fronda

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 40-76 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 40-76 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 September 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 04/21/2006 has been entered.

2. Claims 40-76 are under consideration in this Office Action.

3. Claim 73 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 50. This objection was stated in the previous Office Action but has not been addressed by applicants. This objection is reproduced below.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### *Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 40-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 recites the phrase "increased glucosamine-6-phosphate synthase activity", where the word "increased" is a relative term. It is unclear to what extent the enzymatic activity has to be in order to qualify as having increased glucosamine-6-phosphate synthase activity. Dependent claims 41-76 are also rejected because they do not correct the defect of claim 40.

Amending the claims to recite that the activity of the glucosamine-6-phosphate synthase is increased compared to an unmodified or unaltered wild-type glucosamine-6-phosphate synthase may overcome the rejection.

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***Claim Rejections - 35 U.S.C. § 112, 1st Paragraph***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 40-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants' arguments filed 04/21/2006 have been fully considered but they are not persuasive for reasons of record and for the following additional reasons stated below.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing the claimed modified coding region of a gene encoding glucosamine-6-phosphate synthase that has increased enzyme activity requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities, which would clearly constitute undue experimentation.

Guo et al. (Proc Natl Acad Sci U S A. 2004 Jun 22;101(25):9205-10; PTO 892) teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula  $(.66)^x \times 100\%$  where x is the number of mutations introduced.

Applying this estimate to the *E.coli* glucosamine-6-phosphate synthase having 100 mutation within its amino acid sequence consisting of 609 amino acid residues would result in about  $9 \times 10^{-20} \%$  of random mutants having any activity. Similarly, 50 mutations only about  $9 \times 10^{-10} \%$  would be active, and 25 mutations about  $3 \times 10^{-5} \%$  would be active.

Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants as is the case for an *E.coli* glucosamine-6-phosphate synthase having 25 mutations (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the case for an *E.coli* glucosamine-6-phosphate synthase having 50 mutations would not be possible.

Since a large amount of screening is required, the specification and prior art must provide

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a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided by the instant specification, the declaration of Dr. Deng filed 02/19/2002, and the declaration of Dr. Demain filed 04/21/2006. Furthermore, the specification, the declaration of Dr. Deng filed 02/19/2002, and the declaration of Dr. Demain filed 04/21/2006 do not disclose what domains and motifs within the amino acid sequence of the *E.coli* glucosamine-6-phosphate can be modified to make a glucosamine-6-phosphate synthase that has increased activity compared to an unmodified glucosamine-6-phosphate synthase.

The examiner maintains that general teachings for screening and searching for the glucosamine-6-phosphate synthase with the desired properties is not guidance for making the claimed invention. Without additional guidance regarding the specific type of genetic modification to perform on the specific codons within the coding region of any polynucleotide encoding glucosamine-6-phosphate synthase that lead to the desired increase in enzyme activity or decreased product inhibition, then the experimentation left to those skilled in the art is undue.

8. Claims 40-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' arguments filed 04/21/2006 have been fully considered but they are not persuasive for reasons of record and for the following additional reasons stated below.

As stated in the previous Office Actions the claims are genus claims that are directed toward any microorganism comprising any nucleic acid having any genetic modification that increases glucosamine-6-phosphate synthase activity or reduction of product inhibition of glucosamine-6-phosphate synthase activity, and the use of the claimed microorganism for the production of glucosamine.

The claims are not limited to the *E.coli* glucosamine-6-phosphate synthase of the examples of the instant specification. Instead, the scope of the claimed genus includes many microorganisms, many glucosamine-6-phosphate synthases of any structure and amino acid sequence from any biological source, and many genetic modifications to obtain the desired property. Furthermore, the genus is highly variable because a significant number of structural differences between genus members exists.

As stated in the previous Office Actions, in order to meet the written description requirement, the specification must describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus. The Declaration of Dr. Deng clearly shows in Table 1 that glucosamine-6-phosphate synthase sequences from the other listed biological sources except the *H. influenzae* glucosamine-6-phosphate synthase have low homology to *E.coli*

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glucosamine-6-phosphate synthase. There is no guidance and prediction regarding common regions and/or domains which can be altered in order to increase the enzymatic activity of any glucosamine-6-phosphate synthase from any biological source. Simply stating that common catalytic amino acids are present is insufficient to provide guidance as to where genetic modifications can be made to increase enzyme activity. Thus, the skilled artisan would not be able to predict the structure of other species encompassed by the claimed genus by the single description of the *E.coli* glucosamine-6-phosphate synthase.

Applicants have failed to sufficiently describe the claimed genus, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.


### ***Conclusion***

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

  
**TEKCHAND SAIDHA**  
**PRIMARY EXAMINER**